FDA Briefing Document

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

October 20, 2014

BACKGROUND PACKAGE FOR BLA 125504 COSENTYX (SECUKINUMAB)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought secukinumab to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Division Director Memorandum/Division Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Products
M E M O R A N D U M

Date:	September 22, 2014
From:	Kendall A. Marcus, MD Director, Division of Dermatology and Dental Products Office of Drug Evaluation III, CDER, FDA
To:	Chair, Members and Invited Guests Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)
Subject:	Overview of the October 20, 2014 DODAC meeting

Cosentyx (secukinumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

Secukinumab is a first-in-class, fully human, monoclonal IgG1κ IL17A antibody that selectively binds to the pro-inflammatory cytokine interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis.

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 150 mg SC injections. The proposed presentations for secukinumab SC injection include an autoinjector (AI, the prefilled SensoReady® pen), a prefilled syringe (PFS), and a lyophilized powder in vial (LYO).

I. REGULATORY BACKGROUND AND INTRODUCTION

This document provides the Dermatologic and Ophthalmic Drugs Advisory Committee with a summary of FDA analyses of the data submitted by Novartis to support an indication for secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. During the scheduled October 20, 2014 Advisory Committee meeting, the Committee will be asked to consider the safety and efficacy data submitted in support of the secukinumab application.

The background materials provided represent the preliminary findings and opinions of the multidisciplinary review team and are based on their reviews of the Applicant's submissions. Please note that the FDA analyses presented herein may differ somewhat from those presented by the Applicant. This document represents the review team's preliminary findings to date. No regulatory decision has been made on the status of the application.

The proposed indication is supported by the 52-week safety and efficacy data from the Phase 3 trials CAIN457A2302, CAIN457A2303, (hereafter referred to as 2302 and 2303, respectively in our document) and 12-week safety and efficacy data from the Phase 3 trials CAIN457A2308, and CAIN457A 2309 (hereafter referred to as 2308 and 2309). An additional 6 Phase 2/3trials have been conducted in psoriasis. A safety update report was also provided in support of the current application.

Trials 2302, 2303, 2308 and 2309 were similarly designed to assess two secukinumab doses (150 mg and 300 mg). Trial 2303 included an active comparator arm with a non-US approved biologic (EU-approved etanercept). Comparisons between secukinumab and the active comparator will not be discussed in this document.

All psoriasis trials were conducted in subjects with moderate to severe plaque psoriasis. Six Phase 3 psoriasis trials were completed and are summarized in the table below:

Table 1-1 Summary of phase III studies in psoriasis

Study	Description	Formulation	N	Treatments
Placebo-controlled, active-controlled trials				
A2302 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Lyophilisate in vial	738	150 , 300 mg AIN, PBO[a] qw for 4 wk, then q4w to Wk 48
A2303 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled and active comparator (etanercept) comparison	Lyophilisate in vial	1306	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48 Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51
A2308[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Pre-filled syringe	177	150, 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2309[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Autoinjector / pen	182	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2304 *(52 Wk)*	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment at start of relapse" – maintenance regimen comparison	Lyophilisate in vial	966	150, 300 mg AIN qw for 4 wk, then q4w until Wk 12[b,c] For PASI 75 responders: *Fixed Interval:* induction dose q4w to Wk 48 *Retreatment at start of relapse*[d]: PBO to relapse, then induction dose q4w till PASI 75 then PBO to relapse or Wk 48
A2307 *(40 Wk)*	Efficacy/safety of uptitration in partial responders at Wk 12 from A2304 – dose regimen comparison	Lyophilisate in vial	43	10 mg/kg i.v. or 300 mg s.c. AIN at randomization, Wk 2 and Wk 4, then 300 mg s.c. q4w to Wk 36

N=number of patients randomized
AIN = AIN457/secukinumab; LYO=lyophilisate in vial; PBO = placebo; PASI = Psoriasis Area and Severity Index
[a] = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 or 300 mg AIN and treated from Wk 12 onwards
[b] = PASI nonresponders discontinued study treatment
[c] = partial responders could enter Study A2307
[d] = start of relapse is a loss of ≥ 20% of the max. PASI gained in the study, with a loss of PASI 75 response
[e] = 12 weeks safety data of 52 week study
Source: [Tabular Listing of all Clinical Studies]

Four Phase 2 trials were performed to support dose selection for Phase 3, only one of which included longer term maintenance therapy (150 mg SC q4w) per the following summary table:

Table 1-2 Summary of phase II studies in psoriasis

Study	Description	Formulation	N	Treatments
A2102	Single dose (i.v.) in target population	Lyophilisate in vial	36	3 mg/kg AIN PBO
A2211	Multi-dose regimen finding (s.c.) in target population	Lyophilisate in vial	404	Induction 1 x 150 mg AIN 3 x 150 mg AIN at Wk 1, 5, 9 4 x 150 mg AIN at Wk 1, 2, 3, 5 5 x PBO at Wk 1, 2, 3, 5, 9 Maintenance in responders: *Fixed Interval:* 150 mg at Wk 13, 25 *Start of relapse:* 150 mg AIN, PBO at Wk 13, 25 Treatment in partial or non-responders: *Open label:* 150 mg s.c. q4w AIN until Wk 33
A2212	Multiple-loading dose regimen (i.v.) in target population	Lyophilisate in vial	100*	1 x 3 AIN at Day 1 1 x 10 mg/kg AIN at Day 1 3 x 10 mg/kg AIN at Day 1, 15, 29 3 x PBO at Day 1, 15 , 29
A2220	Dose-ranging (s.c.) in target population	Lyophilisate in vial	125	3 x 150 mg AIN at Wk 1, 5, 9 3 x 75 mg AIN at Wk 1, 5, 9 3 x 25 mg AIN at Wk 1, 5, 9 1 x 25 AIN at Wk 1 PBO at Wk 1, 5, 9
*A2204***	*Single dose (i.v.) in target population*	*Lyophilisate in vial*	*80*	*0.3, 1, or 3 mg/kg AIN* *PBO*

The Applicant is seeking approval for a secukinumab dose of 300 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly dosing starting at Week 4. Each 300 mg dose is given as 2 150 mg SC injections with one of the following proposed formulation and presentations:

−Injection: 150 mg/mL in a single-use prefilled SensoReady pen (AI, autoinjector)

−Injection: 150 mg/mL in a single-use prefilled syringe (PFS)

−Injection, powder for solution: 150 mg in a single-use vial (LYO)

II. SUMMARY OF EFFICACY

Secukinumab (AIN457) 300 mg and 150 mg in lyophilisate in vial (LYO) were superior to placebo in the treatment of moderate to severe plaque psoriasis in two Phase 3 trials (2302 and 2303). The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score ≥12, an Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA) involvement ≥10% at baseline. Trial subjects randomized to receive secukinumab received injections once a week for the first 4 weeks and then once every 4 weeks through Week 52.

The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥ 75% reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12, with a secondary endpoint of PASI 90 response (i.e., ≥ 90% reduction in PASI score) at Week 12. Table 2-1 summarizes the efficacy results for the co-primary endpoints and the secondary endpoints for the two Phase 3 trials.

Table 2-1: Results of the Co-primary and Secondary Efficacy Endpoints at Week 12 for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303		
	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)
Co-primary endpoints						
IGA of clear or almost clear	160 (65%)	125 (51%)	6 (2%)	202 (62%)	167 (51%)	9 (3%)
PASI 75 Response	200 (82%)	174 (71%)	11 (4%)	249 (76%)	219 (67%)	16 (5%)
Secondary endpoint						
PASI 90 response	145 (59%)	95 (39%)	3 (1%)	175 (54%)	137 (42%)	5 (2%)

Both secukinumab 300 mg and 150 mg were superior to placebo ($p<0.0001$) for the co-primary endpoints of PASI 75and IGA of 0 or 1, as well as the secondary endpoint of PASI 90 in each of the pivotal trials.

The patient reported outcomes (PRO) on itching, pain, and scaling were included as secondary endpoints in the testing strategy. However, it should be noted that not all centers had the Psoriasis Diary device available and furthermore, subjects could elect not to use the device at those sites where the device was available. As a result, approximately 40% of subjects from each trial participated in assessing the PRO responses. For those

subjects that reported the PROs, the improvement in the severity of psoriasis disease severity also led to the improvement in itching, pain, and scaling. This was also the case for the subjects who were IGA failures, although the improvements were smaller in magnitude compared to those of the IGA successes.

In addition to Trials 2302 and 2303, which evaluated lyophilized powder in vial (LYO) presentation, the Applicant's development program for secukinumab also included a Phase 3 trial to support the safety and efficacy of secukinumab in liquid formulation in prefilled syringes (2308), and autoinjectors (2309). The same co-primary endpoints were used in all four trials. While the trials showed that both secukinumab doses in prefilled syringes (PFS) and in autoinjectors (AI) were superior to placebo ($p<.0001$), the trials were not designed to address how the efficacies using the PFS or the AI compare to those of the original LYO formulation of secukinumab. However, in comparing the efficacy results across trials, the response rates in Trials 2308 and 2309 were generally similar to those of the Trials 2302 and 2303. Table 2-2 shows the results of the co-primary endpoints at Week 12 for Trials 2308 and 2309.

Table 2-2: Results of the Co-primary Efficacy Endpoints at Week 12 using the Prefilled Syringes (Trial 2308) and Autoinjectors (Trial 2309)

	Trial 2308 (PFS[1])			Trial 2309 (AI[2])		
	AIN457 300 mg (N=59)	AIN457 150 mg (N=59)	Placebo (N=59)	AIN457 300 mg (N=60)	AIN457 150 mg (N=61)	Placebo (N=61)
IGA of clear or almost clear	40 (68%)	31 (53%)	0 (0%)	44 (73%)	32 (52%)	0 (0%)
PASI 75 response	44 (75%)	41 (69%)	0 (0%)	52 (87%)	43 (70%)	2 (3%)

(1) PFS: Prefilled syringes; (2) AI: Autoinjector

In the Biologics License Application (BLA) submission, the Applicant also included results from a Phase 3 trial (2304) that compared two maintenance regimens (i.e., retreatment at start of relapse (SoR) regimen versus the retreatment at fixed interval (FI) regimen), as well as results from a Phase 3 trial (2307) that investigated up-titration in partial responders (i.e., PASI 50 but not PASI 75 responders). However, the primary objective of Trial 2304 was not met as the trial was unable to show that the retreatment at SoR regimen was non-inferior to (i.e., not worse than) the retreatment at FI regimen by the pre-specified non-inferiority (NI) margin of 15% with respect to the PASI 75 response. Furthermore, Trial 2307 was small in size and the primary objective of Trial 2307 was not established as the trial did not show that up-titrating the partial responders with intravenous (i.v.) administration of secukinumab was more efficacious than up-titrating to or prolonging treatment with 300 mg secukinumab. Consequently, these two trials were inconclusive.

III. SUMMARY OF SAFETY

This section will primarily focus on review of the safety data through Week 52 from Trials 2302 and 2303 and data through Week 12 from the Trials 2308 and 2309. As the trial designs were similar, the safety analysis was conducted by pooling the safety data at 12 weeks and 52 weeks. To compare short term safety (12-weeks) between secukinumab and placebo, four randomized, placebo-controlled trials in the target indication (Trials 2302, 2303, 2308 and 2309) were pooled (Pool A, N=2399). To assess longer term safety (52 weeks), data was pooled from 10 Phase 2/3 trials in psoriasis described above in Tables 1-1 and 1-2 (Pool B, N=3993). Follow-up safety data provided in the Safety Update Report was also reviewed. The Division's primary safety analyses evaluated treatment-emergent adverse events (AEs), serious AEs (SAEs), severe and life-threatening AEs, AEs leading to discontinuation, deaths and laboratory abnormalities in the Phase 3 trials. Safety review from non-pivotal trials provides supportive data. In general, the Division agrees with the Applicant's safety assessments. Safety comparisons between secukinumab and the non-US approved active comparator will not be described in detail. The overall safety profile between the products was similar. General aspects pertaining to the safety of secukinumab as comparted to placebo are described below.

A. Deaths

Deaths occurred infrequently in the clinical trials and in all cases, were assessed by investigators as unrelated to study drug. No deaths were reported in the 12-week pooled analysis of Trials 2302, 2303, 2308 and 2309. A total of 6 deaths have been reported up to the date of the database lock (July 31, 2013) across all psoriasis trials. One additional death was subsequently reported in the safety update. The reported causes of death included the following: 1) cerebral hemorrhage; 2) intestinal ischemia; 3) disseminated aspergillosis infection; 4) unknown cause; 5) myocardial infarction; 6) suicide and; 7) alcohol poisoning. No deaths were reported for subjects on placebo. One of the deaths was a completed suicide that occurred during the screening period before study drug was administered. The cases do not appear to represent a treatment-related safety signal at this point in the review.

B. Adverse Events (AEs)

Comparisons between active and placebo arms were consistent through the primary endpoint time point of 12 weeks, but were not consistent in longer term extension assessments. There are differing sample sizes between the active and placebo arms as well as differing durations of therapy for many subjects as time progressed over the 52 weeks of follow-up in long term extension trials. Placebo subjects experienced high efficacy failure rates and dropout rates, and could be placed on active therapy in extension trials. Thus, the numbers of placebo subjects became quite small. A summary of AEs, SAEs and selected risks in the first 12 weeks and over 52 weeks of treatment is shown in Table 3-1 below.

Table 3-1: Adverse Events in psoriasis trials

	First 12 weeks			Entire 52 weeks		
	AIN457 150 mg (N=692) n(%)	AIN457 300mg (N=690) n(%)	Placebo (N=694) n(%)	Any AIN457 150 mg (N=1395) n(IR)	Any AIN457 300 mg (N=1410) n(IR)	Placebo (N=323) n(IR)
Total AEs	412 (60)	388 (56)	340 (49)	1066 (239.90)	1091 (236.10)	413 (351.79)
Total SAEs	14 (2.0)	14 (2.0)	12 (1,7)	76 (6.80)	85 (7.42)	15 (7.54)
Selected risks based on AEs						
Infections and infestations (SOC)	203 (29.3)	195 (28.3)	134 (19.3)	653 (85.29)	704 (91.06)	173 (101.89)
URTIs (HLT)	129 (18.6)	117 (17.0)	72 (10.4)	408 (45.02)	426 (45.39)	96 (52.03)
Candida infections (HLT)	3 (0.4)	8 (1.2)	2 (0.3)	21 (1.85)	41 (3.55)	2 (1.00)
MACE (NMQ)	0 (0.0)	2 (0.3)	0 (0.0)	5 (0.44)	6 (0.51)	1 (0.50)
CCV-related events (NMQ)	7 (1.0)	3 (0.4)	11 (1.6)	30 (2.65)	82 (3.04)	13 (6.54)
Malignant or unspecified tumours (SMQ)	3 (0.4)	1 (0.1)	3 (0.4)	11 (0.97)	9 (0.77)	3 (1.49)
Hypersensitivity (narrow SMQ)	31 (4.5)	31 (4.5)	9 (1.3)	115 (10.70)	132 (11.94)	9 (4.50)
Neutropenia (narrow NMQ)	2 (0.3)	4 (0.6)	0 (0.0)	15 (1.32)	16 (1.37)	0 (0.00)
Crohn's disease (PT)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.18)	0 (0.00)	0 (0.00)

IR=exposure-adjusted incidence rate per 100 patient-years
CCV=cardio-cerebrovascular; HLT=high level term; MACE=major adverse cardiovascular event; NMQ=Novartis MedDRA query; PT=preferred term; SMQ=standardized MedDRA query
SOC=system organ class; URTIs=upper respiratory tract infections

C. Serious Adverse Events (SAEs)

In the 12-week pooled analysis of Trials 2302, 2303, 2308 and 2309, the incidence of SAEs was low and comparable for both doses of secukinumab and placebo (2.0% for both 300 mg and 150 mg vs. 1.7% for placebo). No SAE was reported in any MedDRA System Organ Class (SOC) with greater than 1% frequency. SAEs in selected risks, such as CCV events and malignancies, showed small imbalances for secukinumab and will be discussed further below. Exposure-adjusted rates of SAEs per 100 patient-years over the entire treatment period in all psoriasis trials were comparable across all treatment groups (7.4, 6.8, and 7.5 for 300 mg, 150 mg, and placebo) as well. Many SAEs by preferred term showed a small increase with either secukinumab dose compared with placebo, although the exposure-adjusted rates were

low (≤ 0.22 per 100 patient-years; see Table 3 above). The PT pneumonia was reported by the highest number of subjects 0.2% (6/3430), and was not reported in placebo arm.

D. Common Adverse Events

The absolute incidence of all AEs in the induction period of both Pools A and B was higher with secukinumab (300 mg, 150 mg, or any dose) compared to placebo. The imbalance in total AEs was mainly due to AEs reported from the SOC of infections and infestations and will be discussed further below.

E. Specific Safety Assessments

1. Infections

Observations in humans with genetic defects affecting the Th17 pathway and in individuals who have genetic defects in IL-17 signaling suggest that blockade of IL-17 increases the risk for fungal infections, particularly mucocutaneous candidiasis, as well as staphylococcal skin infections.

In the secukinumab development program, common infections such as nasopharyngitis and upper respiratory tract infection were reported more frequently in the two secukinumab dose groups as compared to placebo. Serious infections were infrequent. One subject in the extension trial 2302E1 was diagnosed with esophageal candidiasis 6 months into the randomized withdrawal study which followed one year of treatment with secukinumab at a dose of 300mg. No cases of treatment-emergent tuberculosis were reported for subjects on secukinumab.

A higher rate of mucocutaneous candida infections with secukinumab, particularly the higher dose, was observed consistently at both 12 weeks and throughout the entire treatment periods. Infections related to candida appear to show both an exposure-response and a dose-response relationship as shown in Table 3-2 below.

Table 3-2: AE Exposure-Response Rate for Safety (Week 52) by Observed Serum Concentration Quartiles

150 mg	Secukinumab concentration range		All (n=396)
	<15.9 mcg/mL (n=197)	≥15.9 to <94.9 mcg/mL (n=199)	
Any AEs	161 (81.7%)	157 (78.9%)	318 (80.3%)
Candida infection	2 (1.0%)	7 (3.5%)	9 (2.3%)

300 mg	Secukinumab concentration range		All (n=414)
	<31.4mcg/mL (n=207)	≥31.4 to <105 mcg/mL (n=207)	
Any AEs	159 (76.8%)	180 (87.0%)	339 (81.9%)
Candida infection	6 (2.9%)	13 (6.3%)	19 (4.6%)

Other adverse events related to infections also demonstrated a dose-response event rate. See Table 3-3. Herpes viral infections (HLT) occurred in a higher proportion of subjects in the 300 mg group than the 150 mg group and were higher than placebo (1.6%, 0.9%, and 0.4% for 300 mg, 150 mg and placebo). No cases of disseminated or CNS herpes were reported. Infections requiring oral or parenteral antimicrobial concomitant treatment were more frequently reported in the 300 mg group than the 150 mg group (12.2% for 300 mg, 9.4% for 150 mg and 7.2% for placebo.

Table 3-3: Adverse Events related to infections reported in psoriasis trials which show a dose-response

Adverse Event	300 mg	150 mg	placebo
Candida infections	1.2%	0.4%	0.3%
Herpes viral infections	1.6%	0.9%	0.4%
Infections requiring antimicrobial treatment	12.2%	9.4%	7.2%

2. Malignancies

At this juncture, there is no evidence that secukinumab confers an increased risk for malignancy. However, since the premarketing trials are of relatively short duration and cannot reliably detect rare events with long latency such as malignancy, the Applicant has proposed a malignancy registry in their risk management plan. The Division finds that postmarketing assessment of malignancy is a reasonable approach.

3. Cardiac Safety Analyses

Subjects with stable cardiovascular risk factors were not excluded from the Phase 2/3 clinical trials that have been submitted to support this BLA. Major adverse cardiovascular events (MACE) [including cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke] were confirmed by an independent

cardiovascular/ cerebrovascular (CCV) adjudication committee. In the first 12 weeks of treatment in psoriasis trials, the rate of MACE was low across all treatment arms. The clustering of CCV SAEs (angina pectoris/ unstable, coronary artery disease/ arteriosclerosis coronary artery, hypertensive crisis, cerebrovascular accident, syncope, [acute] myocardial infarction, palpitations, pulmonary edema, transient ischemic attack, cardiac arrest) in the active secukinumab treatment arms seen over the entire treatment period of 52 weeks for all psoriasis trials was carefully examined. There were differing sample sizes between the active and placebo arms as well as differing durations of therapy for many subjects as time progressed over the 52 weeks of follow-up. Placebo subjects experienced high efficacy failure rates and dropout rates, and could be placed on active therapy in extension trials. Thus, the numbers of placebo subjects became quite small. The Division concurs with the Applicant that there is not a convincing signal for a CV safety concern based on current data.

4. Autoimmunity

Autoimmune diseases represent a heterogeneous group of both organ-specific and systemic diseases. Tumor necrosis factor inhibitors have been associated with the paradoxical development of autoimmune processes thought to be due to a disturbance of immune homeostasis. Thus, autoimmune disorders were evaluated as a group as well as individually. SAEs for autoimmune disorders not related to psoriasis were reported only in secukinumab treatment arms. Pooling of preferred terms of autoimmune disorders resulted in 22 reports of autoimmune diseases (discounting psoriasis and arthropathy) in 3430 subjects treated with any dose of secukinumab. The majority of autoimmune disorders were reported in one subject except for ulcerative colitis (4); Crohn's disease (3); and Basedow's/ Grave's disease (2). Individual cases of autoimmune hepatitis and myelitis were also reported.

5. Hypersensitivity

In these studies, hypersensitivity reactions, including urticaria and angioedema, were reported more frequently in subjects receiving secukinumab than placebo. Although no episodes of life-threatening anaphylaxis reactions were observed in secukinumab's clinical trials, one case occurred in a trial of ankylosing spondylitis. The subject experienced an anaphylactic reaction within 1 hour of the first infusion with 10 mg/kg i.v. secukinumab.

6. Immunogenicity

In the psoriasis Phase 3 trials, 0.4% (10/2842) of subjects developed secukinumab treatment-emergent anti-drug antibodies (ADA). Of the 10 subjects who developed ADAs, 3 subjects were classified as positive for neutralizing antibodies, 5 subjects were classified as negative for neutralizing antibodies, and the remaining 2 subjects were not characterized for neutralizing antibodies status. Overall, no evidence of altered pharmacokinetics (PK), efficacy or safety has

been observed in subjects who developed secukinumab treatment-emergent ADA in psoriasis Phase 3 trials. However, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy and/or safety measures because of the small number of subjects with treatment-emergent ADA.

CLINICAL PHARMACOLOGY SUMMARY

The proposed indication for secukinumab is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 SC injections of 150 mg.

IV. MECHANISM OF ACTION AND PHARMACODYNAMICS

Secukinumab is a human IgG1 monoclonal antibody that binds to the proinflammatory cytokine interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. The serum levels of total IL-17A (free and secukinumab-bound IL-17A) increased following secukinumab treatment in subjects with psoriasis. One hypothesis to explain the increased IL-17A concentrations was that the clearance of IL-17A-secukinumab complex was slower than free IL-17A.

V. PHARMACOKINETICS

In subjects with psoriasis across several clinical trials, the secukinumab clearance values ranged from 0.14 to 0.22 L/day, the terminal half-life values ranged from 22 to 31 days, and the volume of distribution during the terminal log-linear phase ranged from 7.10 to 8.60 L. Following SC administration, secukinumab showed an absolute bioavailability of 55% in a small crossover pharmacokinetic (PK) trial and 73% estimated by population PK analysis. Secukinumab PK was approximately dose proportional for a single dose administration of IV doses from 1 mg/kg to 10 mg/kg and for SC doses from 25 mg to 300 mg.

Body weight was the most significant intrinsic factor for the CL, the central volume of distribution, and the peripheral volume of distribution. Based on the post-hoc estimate of the individual clearance data from the population PK analysis, the mean clearance value in subjects with body weight ≥ 90 kg was approximately 50% higher than that in subjects with body weight < 90 kg. The higher CL in subjects weighing ≥ 90 kg is associated with a lower median serum concentrations compared with those subjects weighing < 90 kg.

VI. DOSE- AND EXPOSURE-RESPONSE RELATIONSHIPS

A. Dose- and Exposure-Response for Efficacy in Phase 3 Trials

Based on the data from two pivotal Phase 3 trials, both univariate and multivariate logistic regression analyses show that secukinumab concentration at Week 12 was a significant predictor of IGA 0/1 response rate at Week 12 (p-value < 2×10^{-16}). In addition to secukinumab exposure, body weight and baseline IGA score were also identified as significant covariates affecting response during multivariate analyses, although the impact of either of these factors was less than that of exposure. The

regression model predicts an increase in response rate of approximately 12% for a two-fold increase in the secukinumab exposure (i.e., the trough concentration). The prediction is similar to the observed difference in response rate between 150 mg and 300 mg (48% and 59% for IGA 0/1 at Week 12 with pooled data from Studies A2302 and A2303) and supports that the observed differences in response rates between secukinumab doses are due to differences in secukinumab exposure.

Similarly, due to the significant effect of body weight on exposure as stated above, subjects with lower body weight (< 90 kg) had a higher response rate compared to subjects with higher body weight (≥ 90 kg) with the same dosing regimen (Figure 1). Within each dose cohort (150 mg or 300 mg), the clinical response rates were approximately 10% higher in the lower body weight group. As an internal comparison, it was also observed that secukinumab efficacy was similar in subjects with body weight < 90 kg who received 150 mg as compared to subjects with body weight ≥ 90 kg who received 300 mg. The observed IGA 0/1 response rate was 50% among 328 subjects who received 150 mg and 52% among 196 subjects who received 300 mg in the two pivotal studies combined.

The exposure-response analysis suggests that IGA 0/1 response rate in patients with body weight ≥ 90 kg administered 300 mg may be further increased if exposures are increased. Population PK simulations suggest that patients with body weight ≥ 90 kg would require 450 mg to achieve similar exposures to that observed in patients with body weight < 90 kg administered 300 mg as shown in Figure 2.

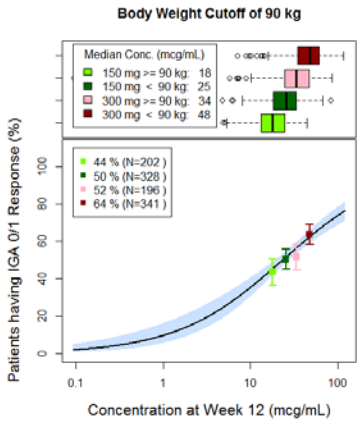

Figure 1: Effect of body weight on secukinumab exposure and IGA 0/1 response using 90 kg as bodyweight cutoff.

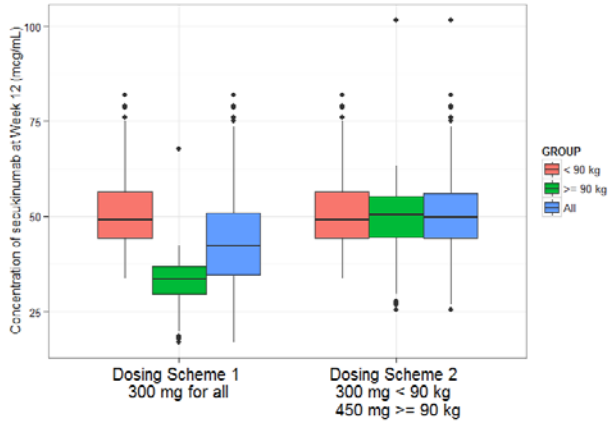

Figure 2: Model-based simulations for trough concentrations at Week 12. Simulations were conducted using the Applicant's population PK model and demographics from CAIN457A2302.

B. Dose- and Exposure-Response for Safety

Pooled analysis of 52-week safety data in the two pivotal Phase 3 trials showed an overall AE rate of 80.3% and 81.9%, respectively, for the 150 mg and 300 mg doses, indicating little to no apparent dose-response for safety. An exploratory safety analysis by exposure quartiles showed a trend of increasing AEs with increasing exposure only at the 300 mg dose. Across the exposure quartiles, the overall AE rates were 75.3%, 88.0%, 84.0% and 73.7% (in an increasing order of the exposure quartile), respectively, for the 150 mg dose, and 72.8%, 80.8%, 83.3% and 87.6%, respectively for the 300 mg dose.

An adverse of event of note, *Candida infections,* showed a trend of increased incidence with increased exposure. In the 150 mg treatment group, there was a trend toward more frequent infections in the two higher exposure quartiles (1.0%, 1.0%, 4.0% and 3.0% in each quartile listed in the order of increasing exposure). In the 300 mg treatment group, a similar trend was observed (1.9%, 3.8%, 6.9% and 5.7% listed in the order of increasing exposure quartile). However, the overall number of events in both treatment groups was small (n=9 for 150 mg and n=19 for 300 mg treatment groups).

VII. BIOPHARMACEUTICS

Each of the proposed 300 mg doses is to be administered as two SC injections of 150 mg in one of the following three proposed to-be-marketed formulations and presentations for secukinumab:

- Injection: 150 mg/mL in a single-use prefilled SensoReady® pen (AI, autoinjector)
- Injection: 150 mg/mL in a single-use prefilled syringe (PFS)
- Injection, powder for solution: 150 mg in a single-use vial (LYO)

Among three proposed to-be-marketed presentations, the LYO and the PFS have been shown to have comparable PK in a dedicated PK comparability study. The Applicant did not conduct a dedicated PK study to evaluate the comparability between the AI and the LYO or the PFS. The PFS and AI presentations contain the same liquid formulation with an identical secukinumab concentration and the same primary syringe; they only differ in the device assembly.

The AI was shown to achieve higher exposures than the LYO and the PFS based on the comparisons of secukinumab trough concentrations across multiple Phase 3 trials. Compared to the LYO, the mean concentrations resulting from the AI were higher across two time-points (Week 4 and Week 12) at both dose levels (10-23% at 150 mg and 19-30% at 300 mg). Compared to the PFS, the mean concentrations resulting from the AI were higher across two time-points (Week 4 and Week 12) at both dose levels (16-18% at 150 mg and 23-26% at 300 mg).

VIII. GENERAL SUMMARY

The currently available data support a favorable benefit-risk assessment for the use of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. No major safety issues associated with secukinumab use have been identified to date.

IX. PRELIMINARY TOPICS FOR THE ADVISORY COMMITTEE

The Division is convening this meeting to solicit the Committee's comments on the following topics. Please note, however, that these are preliminary topics and are still subject to change.

1. **Considering potential risks and benefits, do the available data support approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy?**

   Background Information for Consideration (Issue 1): As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with all of the proposed dosing recommendations or that one must define all labeling recommendations. Questions 2 and 3 that follow the general approval question/vote will give the Committee a chance to provide opinions on more granular issues. If not, please consider what additional studies should be recommended.

2. **Please comment on the strength of evidence for use of secukinumab at a dose strength of 300 mg for all patients independent of weight.**

   Background Information for Consideration (Issue 2): The Phase 3 efficacy results showed that both 150 mg and 300 mg doses of secukinumab achieved significantly higher response rates compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose. At the same dose, secukinumab serum concentrations were higher in subjects with a body weight < 90kg than those in subjects with a body weight ≥ 90 kg, and the clinical response rates were approximately 10% higher in the lower body weight group at both 150 mg and 300 mg doses. A limited number of adverse events, mostly infections, demonstrated an increasing trend with higher exposure. Should the dose strength of secukinumab be reduced to 150 mg in the patient subgroup with body weight <90 kg? Should there be an exploration of the higher dose strength of 450 mg in the patient subgroup with a weight ≥90 kg?

3. **Please comment on postmarketing studies/trials that are needed to further define the safety and/or efficacy of secukinumab, including, but not limited to the need for long-term studies to evaluate malignancy risk and whether alternative dosing strategies should be evaluated.**